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**Title: Metabolic Reprogramming in Cancer: Implications for Immunosuppressive Microenvironment**

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**Title: Metabolic Reprogramming in Cancer: Implications for Immunosuppressive Microenvironment**

**Abstract:** Cancer is a complex and heterogeneous disease characterized by uncontrolled cell growth and proliferation. One hallmark of cancer cells is their ability to undergo metabolic reprogramming, which allows them to sustain their rapid growth and survival. This metabolic reprogramming creates an immunosuppressive microenvironment that facilitates tumour progression and evasion of the immune system. In this paper, we review the mechanisms underlying metabolic reprogramming in cancer cells and discuss how these metabolic alterations contribute to the establishment of an immunosuppressive microenvironment. We also explore potential therapeutic strategies targeting metabolic vulnerabilities in cancer cells to enhance immune-mediated anti-tumour responses.

**Keywords:** Metabolic Reprogramming, Cancer, Immunosuppressive Microenvironment

1. **Introduction** 
   1. **Overview of Cancer Metabolism**

Cancer metabolism refers to the distinct metabolic alterations that occur in cancer cells compared to normal cells.[1] The metabolism of cancer cells directly stems from the alteration of intracellular signalling pathways caused by mutations in oncogenes and tumour suppressor genes.[2] The reprogramming of cellular energy metabolism is increasingly recognized as a fundamental characteristic of cancer and could potentially offer a biochemical foundation for novel therapeutic approaches.[3,4] Significant endeavors in recent years have focused on uncovering the mechanisms behind metabolic changes in cancer, sparking substantial research interest in mitochondria, bioenergetics, and redox regulation in both normal and malignant cells.[3]

While normal cells primarily rely on oxidative phosphorylation (OXPHOS) to generate energy in the form of adenosine triphosphate (ATP), cancer cells exhibit a metabolic phenotype characterized by increased aerobic glycolysis, a phenomenon known as the Warburg effect.[5,6]. This metabolic switch allows cancer cells to preferentially metabolize glucose to lactate, even in the presence of oxygen, which is less efficient in terms of ATP production but provides crucial biosynthetic intermediates essential for supporting rapid cell proliferation and growth.[7,8] Aerobic glycolysis constitutes approximately 56–63% of the ATP production in the majority of cancer cells. These cells increase their uptake of glucose from the surrounding environment and elevate the secretion of lactic acid to fulfill their energy and metabolic needs.[9]

Beyond aerobic glycolysis, cancer cells also exhibit alterations in other metabolic pathways, including enhanced glutamine metabolism, which serves as an additional carbon and nitrogen source to support cell growth and survival. 10] Furthermore, dys-regulated fatty acid metabolism, altered redox homeostasis, and rewired nucleotide metabolism contribute to the metabolic reprogramming observed in cancer.[11] Importantly, cancer metabolism is not solely driven by intrinsic genetic mutations but is also influenced by extrinsic factors within the tumour microenvironment, such as hypoxia, nutrient availability, and interactions with stromal cells.[12] These microenvironmental cues shape the metabolic phenotype of cancer cells and contribute to the heterogeneity observed in tumour metabolism. [13,14,15,16]

Understanding the intricacies of cancer metabolism is essential for elucidating the molecular mechanisms driving tumourigenesis and identifying metabolic vulnerabilities that can be exploited for therapeutic intervention. Moreover, targeting cancer metabolism holds promise for developing novel anti-cancer strategies aimed at disrupting the metabolic dependencies of cancer cells while sparing normal tissues.[17]

* 1. **Importance of Metabolic Reprogramming in Cancer Progression**

Metabolic adaptation allows cancer cells to produce ATP at a higher rate through glycolysis compared to oxidative phosphorylation, despite the presence of oxygen.[18] Despite the less efficient ATP yield per glucose molecule compared to oxidative phosphorylation, glycolysis allows cancer cells to rapidly generate ATP and produce metabolic intermediates needed for cell growth and proliferation.[19] The increased glycolytic flux provides cancer cells with a rapid and efficient means of meeting their energy demands, essential for sustaining their unchecked proliferation and growth.[6]

Beyond ATP generation, metabolic reprogramming enables cancer cells to synthesize macromolecules required for cell growth and division.[20] Cancer cells divert glucose-derived carbon flux towards biosynthetic pathways, supporting the synthesis of nucleotides, lipids, and amino acids necessary for cellular replication and biomass accumulation.[21] By up-regulating anabolic pathways, such as the pentose phosphate pathway (PPP) and de novo lipid synthesis, cancer cells ensure a sufficient supply of building blocks for DNA replication, membrane biogenesis, and protein synthesis.[21,22] Moreover, metabolic intermediates derived from glycolysis and other metabolic pathways serve as precursors for the production of key signalling molecules and post-translational modifications, contributing to the rewiring of signalling networks that drive oncogenic transformation and tumour progression.[23]

Cancer cells experience various stresses within the tumour microenvironment, including oxidative stress, nutrient deprivation, and hypoxia. Metabolic reprogramming allows cancer cells to adapt to these challenges by modulating redox homeostasis and cellular stress responses. [24] For instance, alterations in glucose metabolism and mitochondrial function influence the production of reactive oxygen species (ROS) and cellular antioxidant capacity, impacting the balance between oxidative damage and cellular survival.[25] Additionally, metabolic adaptations enable cancer cells to utilize alternative nutrient sources, such as glutamine and fatty acids, to sustain their metabolic requirements under nutrient-restricted conditions.[26] Importantly, metabolic reprogramming contributes to the establishment of an immunosuppressive tumour microenvironment, which facilitates immune evasion and tumour immune escape.[27]

Cancer cells secrete metabolites, such as **lactate, adenosine, and kynurenine**, which modulate immune cell function and suppress anti-tumour immune responses.[28] These metabolites exert pleiotropic effects on various immune cell populations, including T cells, natural killer (NK) cells, and antigen-presenting cells (APCs), impairing their effector functions and promoting the expansion of immunosuppressive cell subsets, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[29] Moreover, metabolic competition between cancer cells and immune cells for nutrients within the tumour microenvironment further dampens anti-tumour immunity and promotes immune tolerance.[30]

* 1. **Role of the Tumour Microenvironment in Immune Evasion**

The tumor microenvironment (TME) plays a crucial role in immune evasion, a key mechanism by which tumors escape the host immune response. [13] The TME is a complex and dynamic milieu composed of cancer cells, stromal cells, immune cells, blood vessels, extracellular matrix (ECM), and various signaling molecules.[13, 31] This intricate environment fosters an immunosuppressive niche that protects tumor cells from immune surveillance and destruction. Several factors contribute to this immunosuppressive microenvironment. [13, 32, 33] Firstly, cancer-associated fibroblasts (CAFs) and myeloid-derived suppressor cells (MDSCs) within the TME secrete immunosuppressive cytokines like TGF-β and IL-10, which inhibit the activity of cytotoxic T cells and natural killer (NK) cells, pivotal for anti-tumor immunity [13, 32, 33, 34]. Secondly, the expression of immune checkpoint molecules such as PD-L1 on tumor cells and stromal cells binds to PD-1 receptors on T cells, leading to T cell exhaustion and impaired immune response. [13, 32, 33, 34]Furthermore, the hypoxic conditions prevalent in the TME induce the expression of hypoxia-inducible factors (HIFs) that promote angiogenesis and metabolic reprogramming, further facilitating immune evasion. The TME also supports the recruitment and differentiation of regulatory T cells (Tregs), which suppress the activation and proliferation of effector T cells. [13, 34]Additionally, the dense ECM and irregular vascularization create physical barriers that impede the infiltration of immune cells into the tumor core. Understanding the complex interactions within the TME is critical for developing therapeutic strategies that can effectively modulate the immune landscape, enhance anti-tumor immunity, and overcome immune resistance. [35, 36] This knowledge is fundamental to the advancement of immunotherapies and their integration into comprehensive cancer treatment regimens

1. **Metabolic Reprogramming in Cancer Cells**

**2.1 Aerobic Glycolysis (Warburg Effect)**

Aerobic glycolysis, famously termed the Warburg effect after Otto Warburg's pioneering observations, represents a fundamental metabolic adaptation in cancer cells. Unlike normal cells, which predominantly rely on oxidative phosphorylation (OXPHOS) for ATP production by oxidation of pyruvate in the mitochondria, cancer cells exhibit a pronounced preference for glycolysis as their primary energy-generating pathway.[37] Specifically, the 'Warburg Effect' manifests in numerous human tumours, making positron emission tomography (PET) with the glucose analogue 18F-fluorodeoxyglucose a commonly employed method for clinical tumour imaging. [38,39] This metabolic switch allows cancer cells to rapidly metabolize glucose to lactate, generating ATP more quickly than through OXPHOS, despite the less efficient yield of ATP per glucose molecule.[37] The Warburg effect not only provides cancer cells with a rapid source of energy but also generates metabolic intermediates essential for biomass synthesis and cellular proliferation.[40] Beyond its role in energy metabolism, aerobic glycolysis enables cancer cells to adapt to the dynamic tumour microenvironment by facilitating the production of lactate, which serves as a signalling molecule and modulates various aspects of tumour progression, including angiogenesis, immune evasion, and metastasis.[6] Moreover, recent studies have revealed that the Warburg effect is regulated by a complex interplay of signalling pathways and metabolic enzymes, highlighting its significance as a potential therapeutic target in cancer treatment.[41,42] However,it is important to remember that, some cancer cells do utilize oxidative phosphorylation, especially in regions with adequate oxygen supply.[43].Therefore metabolic profile of cancer cells can vary significantly between different types and even within a single tumour.

**2.2 Glutamine Metabolism**

Glutamine, a non-essential amino acid, plays a central role in cancer metabolism, serving as a versatile substrate for various biosynthetic and energy-producing pathways.[44] In cancer cells, glutamine metabolism is often up-regulated to meet the increased demands for nutrients and energy required for rapid proliferation.[45] Cancer cells actively import glutamine through specialized amino acid transporters, and within the mitochondria, it undergoes enzymatic conversion to glutamate catalyzed by two forms of the glutaminase enzyme: kidney-type glutaminase (GLS)1 and liver-type GLS2.[46] Elevated expression of GLS1 is observed in different cancer cell types, and this characteristic is linked to advanced disease stages and unfavorable prognostic outcomes.[47]

Glutamate serves as a precursor for the synthesis of other amino acids, nucleotides, and antioxidant molecules, supporting the anabolic demands of proliferating cancer cells. [48] Glutamate can be converted into various non-essential amino acids through transamination reactions, a process where the amino group is transferred to another molecule.[49] This is particularly important for cancer cells as they often have increased demands for certain amino acids to build proteins and other essential molecules.[50] Glutamate can also be converted into glutathione, a crucial antioxidant that protects cells from damage caused by free radicals. Cancer cells are often under increased oxidative stress, and glutathione plays a role in mitigating this damage and promoting survival.[51]

Moreover, glutamine-derived α-ketoglutarate where glutamine is converted to glutamate, which is further converted to α-ketoglutarate through the process of glutaminolysis enters the tricarboxylic acid (TCA) cycle, replenishing intermediate, sustaining mitochondrial metabolism and nucleotide biosynthesis, helping cancer cells replicate their DNA and RNA during rapid cell division.[52]The TCA cycle requires several intermediates to function, and α-ketoglutarate is one of them. By entering the cycle, it helps maintain the proper levels of these intermediates and ensures the cycle continues to operate.[52] The TCA cycle is a key part of mitochondrial metabolism, generating energy through ATP production. α-ketoglutarate's contribution to the cycle helps ensure this energy production continues. [53]This process, not only provides cancer cells with a source of carbon for anabolic pathways but also contributes to the maintenance of redox homeostasis and the production of ATP through oxidative phosphorylation [26] However, not all cancer cells rely on glutamine, while glutamine metabolism is important for many cancers, some can utilize alternative pathways or have lower dependence on glutamine specifically.[39]

Additionally, glutamine metabolism is intricately linked to signalling pathways regulating cell growth and survival, with glutamine-derived metabolites serving as key mediators of oncogenic signalling cascades.[54] Dysregulated glutamine metabolism has been implicated in various aspects of tumour biology, including tumour growth, metastasis, and resistance to therapy, making it an attractive target for cancer therapy.[55,56]Therefore pharmacological inhibitors targeting glutamine metabolism have shown promising results in preclinical studies and are being evaluated in clinical trials as potential anticancer agents.[26,57,58]

**2.3 Fatty Acid Metabolism**

Fatty acid metabolism plays a crucial role in fueling the energetic and biosynthetic needs of cancer cells, contributing to their malignant phenotype.[59,60]Unlike normal cells, which primarily rely on glucose as their main energy source, cancer cells exhibit dysregulated lipid metabolism characterized by increased uptake, synthesis, and utilization of fatty acids.[60,61] This metabolic reprogramming enables cancer cells to satisfy the heightened demand for lipids required for membrane synthesis, energy production, and signalling pathways crucial for proliferation and survival [23,59,60,61,62] Fatty acids are acquired either from exogenous sources, such as the circulation, or synthesized de novo from precursor molecules, including glucose, glutamine, and acetate.[63.64] Within cancer cells, fatty acids undergo enzymatic modifications, including β-oxidation and esterification, to generate ATP, produce **signalling molecules like eicosanoids**, and generate phospholipid species essential for membrane integrity and function.[60,65]Moreover, fatty acid metabolism intersects with other metabolic pathways, including glycolysis and the tricarboxylic acid (TCA) cycle, through shared intermediates and regulatory nodes, enabling metabolic flexibility and adaptation to fluctuating nutrient availability. Furthermore, fatty acid metabolism intricately intersects with various other metabolic pathways, such as glycolysis and the tricarboxylic acid (TCA) cycle, via shared intermediates and regulatory points.[66,67] This interconnectedness facilitates metabolic flexibility, allowing cells to adapt to changes in nutrient availability. For instance, intermediates generated during fatty acid metabolism can enter glycolysis or the TCA cycle, serving as additional energy sources or substrates for biosynthetic processes.[68] Additionally, regulatory molecules involved in fatty acid metabolism may influence the activity of enzymes in glycolysis or the TCA cycle, contributing to the coordinated control of cellular metabolism.[69]

This intricate network of metabolic pathways enables cells to efficiently utilize diverse nutrients and adjust their metabolic fluxes in response to varying environmental conditions, ensuring optimal cellular function and survival.[70] Dysregulated fatty acid metabolism has been implicated in various aspects of tumour biology, including tumour growth, metastasis, and resistance to therapy, making it an attractive target for cancer treatment.[71] Furthermore, altered lipid metabolism extends beyond fatty acid synthesis to include changes in cholesterol metabolism, lipid droplet dynamics, and lipid signalling pathways, which collectively influence membrane integrity, intracellular signalling, and tumour progression.[60] Indeed, pharmacological inhibitors targeting key enzymes and transporters involved in fatty acid metabolism have shown promising results in preclinical studies and are currently under investigation in clinical trials as potential anticancer agents. [60,72] **(figure 1)**

**2.4 Altered Redox Homeostasis**

Redox homeostasis, the balance between oxidants and antioxidants within cells, is perturbed in cancer cells due to metabolic reprogramming and increased oxidative stress. Cancer cells exhibit heightened levels of ROS production, resulting from aberrant mitochondrial metabolism, oncogenic signalling, and environmental stressors within the tumour microenvironment.[73]This elevated ROS production serves as a double-edged sword, promoting tumour progression through the activation of pro-survival signalling pathways while simultaneously inducing oxidative damage to cellular macromolecules, including DNA, proteins, and lipids.[74] To cope with increased oxidative stress, cancer cells upregulate antioxidant defences, including enzymatic antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants such as glutathione and vitamins C and E.[75]However, despite these adaptive responses, cancer cells often maintain a state of chronic oxidative stress, which contributes to genomic instability, tumour heterogeneity, and therapeutic resistance. Moreover, altered redox homeostasis in cancer cells impacts various aspects of tumour biology, including proliferation, survival, angiogenesis, metastasis, and immune evasion.[76,77] Targeting redox-dependent vulnerabilities in cancer cells represents a promising therapeutic approach, with several antioxidant-based strategies and redox-modulating agents as therapeutic model in investigations.[78]

**2.5 Other Metabolic Pathways Dysregulated in Cancer**

In addition to aerobic glycolysis, glutamine metabolism, fatty acid metabolism, and altered redox homeostasis, cancer cells exhibit dysregulation in several other metabolic pathways crucial for sustaining their malignant phenotype[6] One such pathway is the pentose phosphate pathway (PPP), which generates ribose-5-phosphate and NADPH, essential for nucleotide synthesis and antioxidant defense, respectively.[79]Cancer cells often upregulate PPP activity to support their rapid proliferation and mitigate oxidative stress.[22]Also, altered amino acid metabolism, including increased uptake and catabolism of certain amino acids such as serine, glycine, and methionine, provides cancer cells with essential precursors for protein synthesis, one-carbon metabolism, and redox regulation.[80]Additionally, dysregulated nucleotide metabolism, characterized by increased demand for nucleotides to support DNA replication and repair, drives the activation of salvage pathways and de novo nucleotide synthesis in cancer cells. [81]Beyond these canonical metabolic pathways, cancer cells also exhibit rewired pathways involved in autophagy, mitochondrial metabolism, and epigenetic regulation, which contribute to their metabolic adaptability and survival in adverse microenvironmental conditions.[3,82,83,84]

1. **Immunomodulatory Effects of Metabolic Reprogramming**

**3.1 Generation of Metabolites with Immunoregulatory Properties**

Metabolic reprogramming in cancer cells exerts profound effects on the function and behaviour of immune cells within the tumour microenvironment (TME), shaping the dynamics of anti-tumour immune responses. One key aspect of this modulation is the alteration of nutrient availability and metabolic competition between cancer cells and immune cells.[30]Cancer cells avidly consume nutrients, including glucose, glutamine, and amino acids, to fuel their rapid growth and proliferation, creating a nutrient-deprived microenvironment that compromises the function of infiltrating immune cells.[85]Tumour-associated immune cells, such as T cells, natural killer (NK) cells, and dendritic cells, rely on these nutrients for their activation, proliferation, and effector functions.[86] As a result, metabolic competition within the TME limits the metabolic fitness and anti-tumour activity of immune cells, leading to immune dysfunction and tumour immune evasion.[85]

Furthermore, metabolic reprogramming in cancer cells generates metabolites and metabolic byproducts that directly modulate immune cell function. (For instance, lactate, a product of aerobic glycolysis in cancer cells, accumulates within the TME and acts as an immunosuppressive metabolite.[6,87] Lactate inhibits the cytotoxic activity of T cells and NK cells, impairs dendritic cell maturation and antigen presentation, and promotes the expansion of immunosuppressive cell populations, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[88]Similarly, alterations in amino acid metabolism, such as increased consumption of tryptophan and arginine by cancer cells, result in the depletion of these essential amino acids within the TME, leading to immune suppression and T cell dysfunction.[89] Furthermore, lactate contributes to the acidification of the tumour microenvironment, creating a hostile milieu that hinders immune cell function and promotes immune escape.[90,91]

Another immunoregulatory metabolite produced by cancer cells is adenosine, a purine nucleoside generated from ATP breakdown. [92] Adenosine acts as a potent immunosuppressive molecule by binding to adenosine receptors on immune cells, including T cells and dendritic cells, and inhibiting their activation and effector functions.[92,93] Cancer cells exploit this mechanism to dampen anti-tumour immune responses and facilitate immune evasion. Moreover, adenosine contributes to the generation of an immunosuppressive microenvironment by promoting the recruitment and activation of immunosuppressive cell populations, such as Tregs and MDSCs.[94]

**3.2 Regulation of Immune Checkpoints**

Immune checkpoints are critical regulators of the immune response, serving as molecular brakes that prevent excessive immune activation and maintain self-tolerance.[95]However, cancer cells exploit these checkpoints to evade immune surveillance and promote tumour growth. Metabolic reprogramming in cancer cells plays a pivotal role in the dysregulation of immune checkpoint signalling, contributing to tumour immune evasion and resistance to immunotherapy.[27,96]

One of the most well-characterized immune checkpoint pathways is the programmed cell death protein 1 (PD-1) pathway, which is activated upon interaction with its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2).[97] Cancer cells often upregulate the expression of PD-L1 as part of their immunosuppressive strategy, thereby engaging PD-1 receptors on T cells and inhibiting their effector functions.[98] Notably, metabolic alterations in cancer cells, such as increased aerobic glycolysis and glutamine metabolism, have been shown to regulate the expression of PD-L1 through various mechanisms.[11] For instance, glycolytic intermediates and metabolites, such as lactate and adenosine triphosphate (ATP), can promote PD-L1 expression via activation of signalling pathways, such as the PI3K/Akt/mTOR pathway, and transcriptional regulators, such as hypoxia-inducible factor 1-alpha (HIF-1α).[99] Similarly, glutamine metabolism fuels the synthesis of nucleotides and amino acids necessary for PD-L1 expression and immune evasion.[26]

Additionally, metabolic reprogramming in cancer cells influences the expression and function of other immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and lymphocyte activation gene 3 (LAG-3), which regulate T cell activation and tolerance.[27] Dysregulated lipid metabolism, for instance, can modulate the composition and biophysical properties of the plasma membrane, impacting the spatial organization and signalling activity of immune checkpoint receptors and their ligands.[100] Moreover, alterations in redox homeostasis and reactive oxygen species (ROS) production within the tumour microenvironment can affect immune checkpoint signalling by influencing the stability and turnover of checkpoint molecules and their downstream signalling cascades.[24]

1. **Therapeutic Targeting of Metabolic Vulnerabilities in Cancer**

**4.1 Metabolic Inhibitors as Anti-Cancer Agents**

One class of metabolic inhibitors that has garnered considerable attention is inhibitors of glycolysis, the process by which cancer cells metabolize glucose to generate ATP and biosynthetic intermediates.[4,101] Small molecule inhibitors targeting key enzymes in the glycolytic pathway, such as hexokinase, phosphofructokinase, and pyruvate kinase, have demonstrated efficacy in preclinical studies and are being evaluated in clinical trials for various cancer types [102] For example, inhibitors of lactate dehydrogenase (LDH), which catalyzes the conversion of pyruvate to lactate, have shown promise in limiting tumour growth and metastasis by disrupting lactate production and the acidification of the tumour microenvironment.[103,104]

Another approach involves targeting glutamine metabolism, a hallmark of cancer characterized by increased glutamine uptake and utilization to support biosynthesis, redox balance, and energy production.[26] Glutaminase inhibitors, which block the conversion of glutamine to glutamate, have shown efficacy in preclinical models of cancer, particularly in tumours with high glutamine dependency, such as MYC-driven cancers. Moreover, inhibitors targeting enzymes involved in glutamine utilization, such as glutamate dehydrogenase and glutamine synthetase, are being explored as potential therapeutic agents for cancer.[26] Drugs targeting fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), and fatty acid oxidation (FAO) enzymes have shown efficacy in preclinical models of cancer and are being investigated in clinical trials as monotherapy or in combination with other anti-cancer agents.[105] The production of lipogenic enzymes is increased in tumours such as lung cancer, colorectal cancer, and ovarian cancer.[106]

Furthermore, inhibitors of redox metabolism, such as antioxidants and reactive ROS modulators, have shown potential as anti-cancer agents by disrupting the redox balance in cancer cells and inducing oxidative stress-mediated cell death.[107] These agents target enzymes involved in antioxidant defence mechanisms, such as glutathione peroxidase and thioredoxin reductase, or modulate ROS production through inhibition of mitochondrial respiration or activation of pro-oxidant pathways.

**4.2 Combination Therapies Targeting Metabolism and Immunity**

There is a significant interplay between metabolism and immunity within the TME plays a crucial role in tumour growth, immune evasion, and therapeutic responses. Combining therapies that target both metabolic vulnerabilities and immune checkpoints holds promise for enhancing anti-tumour immunity and improving clinical outcomes in cancer patients.[108]

One approach involves combining metabolic inhibitors with immune checkpoint inhibitors (ICIs) to synergistically enhance anti-tumour immune responses.[109]..Metabolic inhibitors, such as glycolysis inhibitors, glutaminase inhibitors, or fatty acid synthesis inhibitors, disrupt the metabolic pathways that fuel tumour growth and immune evasion, creating a more favorable TME for immune cell infiltration and function.[110] Concurrent administration of ICIs, such as antibodies targeting programmed cell death protein 1 (PD-1) or cytotoxic T lymphocyte-associated n 4 (CTLA-4), unleashes the anti-tumour activity of effector T cells, which have been reinvigorated by metabolic reprogramming. Preclinical studies and early-phase clinical trials have demonstrated promising results with this approach, showing enhanced tumour regression and prolonged survival in various cancer models and patient populations.[111]

Another strategy involves combining metabolic inhibitors with adoptive cell therapy (ACT), such as chimeric antigen receptor (CAR) T cell therapy or tumour-infiltrating lymphocyte (TIL) therapy, to augment the efficacy of immune cell-based treatments.[112,113]Metabolic inhibitors can be used to precondition tumour cells or enhance the metabolic fitness of adoptively transferred immune cells, improving their persistence, functionality, and anti-tumour activity within the TME. [114] Combinatorial approaches that integrate metabolic modulation with ACT have shown synergistic effects in preclinical models and early-phase clinical trials, leading to improved response rates and durable remissions in patients with refractory cancers.[110]

Moreover, combination therapies targeting metabolism and immuno-metabolism hold promise for overcoming resistance mechanisms and improving response durability in cancer treatment.[115]By simultaneously targeting metabolic vulnerabilities in cancer cells and modulating immune cell metabolism and function, these combinatorial approaches create a hostile TME for tumour growth and immune evasion while enhancing the anti-tumour activity of immune effector cells.[94] Furthermore, rational design of combination regimens based on tumour-specific metabolic profiles and immune signatures may enable personalized and precision medicine approaches to cancer therapy, maximizing therapeutic efficacy while minimizing off-target effects and toxicity.

**4.3 Personalized Approaches Based on Metabolic Profiles**

Cancer is a heterogeneous disease characterized by diverse metabolic alterations across different tumour types and individual patients. Personalized approaches that leverage the unique metabolic profiles of tumours offer the potential to optimize treatment strategies and improve clinical outcomes by targeting specific metabolic vulnerabilities.

One aspect of personalized cancer therapy involves comprehensive profiling of tumour metabolism using advanced imaging techniques, metabolomics, and genomic analyses. [116] By characterizing the metabolic phenotype of individual tumours, including alterations in glucose metabolism, amino acid metabolism, lipid metabolism, and redox homeostasis, clinicians can identify specific metabolic dependencies that drive tumour growth and progression. [3] This information enables the selection of tailored therapeutic interventions that target the most critical metabolic pathways driving tumour survival and proliferation.

Furthermore, molecular profiling of tumours can identify specific genetic mutations, oncogenic drivers, and signalling pathways that contribute to metabolic reprogramming in cancer cells. [11]For example, tumours with mutations in genes encoding metabolic enzymes or regulators, such as isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), or phosphoinositide 3-kinase (PI3K), may exhibit distinct metabolic vulnerabilities that can be exploited for therapeutic intervention.[117] Targeted therapies directed against these specific molecular alterations, such as IDH inhibitors or PI3K inhibitors, offer personalized treatment options for patients with tumours harboring these genetic abnormalities.[118]

Moreover, integrating metabolic profiling with immune profiling of the tumour microenvironment (TME) can inform personalized immunotherapy strategies tailored to individual patients.[119] Tumours with specific metabolic phenotypes, such as high glycolytic activity or elevated lactate production, may create an immunosuppressive microenvironment that hinders anti-tumour immune responses. Combination therapies that target both tumour metabolism and immune checkpoints can be personalized based on the metabolic and immune profiles of individual tumours, with the goal of enhancing anti-tumour immunity and overcoming immune evasion mechanisms.[120]

In addition to targeted therapies and immunotherapies, lifestyle interventions and dietary modifications tailored to individual metabolic profiles may complement standard cancer treatments and improve therapeutic outcomes. Nutritional strategies that modulate glucose, amino acid, and lipid metabolism, such as ketogenic diets or caloric restriction, have shown potential to synergize with conventional therapies and enhance their efficacy by targeting metabolic vulnerabilities in cancer cells.[102,121]

1. **Future Directions and Challenges**

**5.1 Unraveling Complex Metabolic Interactions in the Tumour Microenvironment**

Despite significant advancements in our understanding of cancer metabolism, numerous challenges remain in deciphering the intricate metabolic interactions within the tumour microenvironment (TME). Tumour cells exist in a dynamic ecosystem characterized by complex cellular and molecular interactions, which profoundly influence tumour growth, progression, and therapeutic responses. Unravelling the complexity of metabolic interactions within the TME represents a critical area of future research and presents several challenges.[122]

First, the heterogeneity of the TME poses a significant obstacle to unravelling metabolic interactions, as different regions of the tumour may exhibit distinct metabolic phenotypes and dependencies.[123] Tumour heterogeneity arises from genetic, epigenetic, and microenvironmental factors, leading to spatial and temporal variations in metabolic activities and nutrient utilization.[124] Comprehensive profiling of metabolic heterogeneity within tumours using advanced imaging techniques, single-cell sequencing, and spatial transcriptomics is essential to elucidate the diverse metabolic landscapes and identify targetable vulnerabilities.[125]

Second, the crosstalk between cancer cells, stromal cells, immune cells, and the extracellular matrix (ECM) in the TME shapes metabolic adaptations and influences tumour progression.[13,126] Bidirectional communication between tumour cells and stromal cells, such as cancer-associated fibroblasts (CAFs) and tumour-associated macrophages (TAMs), modulates nutrient availability, metabolic reprogramming, and immune evasion strategies.[126,127]

Third, the impact of systemic metabolism and host factors on tumour metabolism and therapeutic responses remains poorly understood.[128] Metabolic alterations in distant organs, such as the liver, adipose tissue, and microbiota, can influence tumour growth and metastasis through systemic effects on nutrient availability, inflammatory signalling, and immune regulation.[129]Moreover, host factors, such as age, sex, and genetic background, can modulate tumour metabolism and treatment outcomes, highlighting the importance of considering host-tumour interactions in cancer research and therapy.[130,131]

Addressing these challenges will require interdisciplinary collaborations and innovative approaches that integrate multi-omics analyses, computational modelling, and experimental validation in preclinical models and clinical settings. [132] .Furthermore, the development of novel technologies for real-time monitoring of metabolic dynamics in live tumours and non-invasive imaging of metabolic biomarkers will facilitate longitudinal studies of tumour metabolism and treatment responses. [133]

**5.2 Developing Novel Therapeutic Strategies Targeting Metabolic Dependencies**

As our understanding of cancer metabolism continues to evolve, there is growing recognition of the potential for targeting metabolic dependencies as a promising strategy for cancer therapy. However, translating this knowledge into effective therapeutic interventions presents several challenges and opportunities for future research:

One challenge lies in identifying and validating novel metabolic targets that are specific to cancer cells and essential for their survival and proliferation.[134].While numerous metabolic vulnerabilities have been identified in cancer cells, including alterations in glycolysis, glutamine metabolism, and lipid synthesis, it is essential to prioritize targets that are selective for cancer cells over normal tissues.[3]High-throughput screening techniques, functional genomics approaches, and computational modelling can aid in the discovery and validation of novel metabolic targets with therapeutic potential.[135]

Another challenge is developing small molecule inhibitors and other targeted therapies that selectively disrupt cancer cell metabolism while sparing normal cells.[11,136] Many metabolic pathways are conserved across different cell types and play essential roles in physiological processes, posing challenges for achieving tumour-specific inhibition without causing off-target effects or systemic toxicity. Rational drug design strategies, such as structure-based drug design and fragment-based screening, can facilitate the development of selective metabolic inhibitors with improved efficacy and safety profiles.[11]

Furthermore, combinatorial approaches that target multiple metabolic pathways or combine metabolic inhibitors with other therapeutic modalities, such as chemotherapy, radiation therapy, or immunotherapy, hold promise for overcoming resistance mechanisms and improving treatment outcomes in cancer patients. Synergistic interactions between metabolic inhibitors and conventional therapies can exploit vulnerabilities in cancer cells and enhance therapeutic efficacy through complementary mechanisms of action.[137] Rational design of combination regimens based on tumour-specific metabolic profiles and molecular signatures may enable personalized and precision medicine approaches to cancer therapy, maximizing therapeutic benefit while minimizing adverse effects.[138]

Moreover, developing innovative drug delivery systems and precision medicine approaches, such as nanoparticle-based drug delivery platforms and patient-derived organoid models, can enhance the efficacy and specificity of metabolic-targeted therapies. [139] These technologies enable targeted delivery of therapeutic agents to tumour cells while minimizing systemic exposure and off-target effects, offering the potential for more effective and personalized cancer treatment strategies.

**5.3 Overcoming Resistance to Metabolic-Targeted Therapies**

While metabolic-targeted therapies hold promise for cancer treatment, the development of resistance presents a significant challenge that limits their long-term efficacy. Resistance mechanisms can arise through various adaptive responses of cancer cells to metabolic stress, necessitating the identification of strategies to overcome resistance and improve treatment outcomes.[140]

One major mechanism of resistance to metabolic-targeted therapies involves the activation of compensatory metabolic pathways that bypass the inhibited pathway and sustain cancer cell survival and proliferation. [141]Understanding the adaptive metabolic rewiring that occurs in response to therapy is critical for identifying rational combination strategies that target multiple metabolic pathways simultaneously, thereby preventing the emergence of resistance.[142]

Another mechanism of resistance involves genetic or epigenetic alterations that confer resistance to metabolic inhibitors. [143]. For instance, mutations in metabolic enzymes or regulatory genes can disrupt drug binding or enzymatic activity, rendering cancer cells insensitive to therapy.[3,144] Moreover, epigenetic changes, such as alterations in DNA methylation or histone modifications, can modulate gene expression patterns and metabolic phenotypes, promoting resistance to metabolic-targeted therapies.[145].Strategies to overcome genetic and epigenetic resistance mechanisms may involve the development of next-generation inhibitors that target alternative metabolic nodes or the combination of metabolic inhibitors with epigenetic modulators to restore sensitivity to therapy. [146,147] Developing strategies to modulate the TME and enhance anti-tumour immune responses may overcome resistance and improve treatment outcomes.

1. **Conclusion**

Metabolic reprogramming is a hallmark feature of cancer, characterized by alterations in cellular metabolism to support the rapid proliferation and survival of malignant cells. This metabolic rewiring not only sustains the energetic and biosynthetic demands of cancer cells but also plays a critical role in shaping the immunosuppressive TME. By consuming nutrients and releasing metabolic byproducts, such as lactate and ROS, cancer cells create an environment that impairs the function of immune effector cells and promotes the expansion of immunosuppressive cell populations, including Tregs and MDSCs. Furthermore, dysregulated metabolism in cancer cells influences the availability of nutrients and metabolites within the TME, depriving neighbouring immune cells of essential nutrients and impairing their effector functions. Additionally, metabolic alterations in cancer cells modulate signalling networks and molecular pathways that regulate immune cell activation and differentiation, further contributing to immune evasion and tumour progression. Understanding the implications of metabolic reprogramming for the immunosuppressive microenvironment is crucial for developing effective cancer therapies that target metabolic vulnerabilities and enhance anti-tumour immune responses. By disrupting the metabolic interactions between cancer cells and the immune system, researchers can develop innovative strategies to overcome immune evasion mechanisms and improve patient outcomes in cancer treatment. Continued research into the metabolic regulation of the TME and the development of novel therapeutic modalities hold the potential to revolutionize cancer treatment and improve outcomes for patients.

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**Figure 1:**

Schematics illustrating the reprogrammed metabolism in cancer cells, highlighting anaerobic glycolysis, also known as the Warburg effect. In cancer cells, glycolysis breaks down glucose into pyruvate, which is predominantly fermented to lactate. The flux of pyruvate through the TCA cycle is significantly down-regulated. Additionally, pathways branching off from glycolysis provide essential biochemical building blocks to support the high proliferation rate of cancer cells.